Continuing Medical Education

Non-opioid strategies for acute pain management

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THE goal of postoperative pain relief is to achieve optimal analgesia, facilitating a quick return to normal physiological organ function with minimal side effects. In addition, the effective treatment of acute postoperative pain may reduce the incidence of chronic pain after surgery. Acute pain management services have progressed, albeit insufficiently in Canadian academic hospitals as reviewed by Goldstein *et al.*,[1] and the use of "multimodal" or "balanced" analgesia – a combination of opioids, non-steroidal anti-inflammatory drugs (NSAIDs), local anesthetics and other adjuvants – has been recommended to manage postoperative pain. Recently, White[2] and Power[3] reviewed the evidence for such pain management. They show that multimodal analgesia improves the efficacy of pain relief, decreases the risk of side effects and is an evidence-based, established strategy for postoperative pain management.[2,3] This Continuing Medical Education (CME) module focuses on the various classes of drugs that have been proposed, in conjunction with other modalities, for acute pain management.

1 Non-steroidal anti-inflammatory drugs

The analgesic, anti-inflammatory, and antipyretic effects of NSAIDs as well as their most notable side effects are attributed to inhibiting cyclooxygenases (COX)-1 and -2, thereby reducing production of mediators of the acute inflammatory response. Traditional NSAIDs such as diclofenac, ketorolac or ibuprofen are widely prescribed as analgesics and anti-inflammatory agents due to their inhibition of prostanoids synthesis through blockade of both COX-1 and COX-2. In an effort to minimize the potential for bleeding at the surgical site and to reduce the incidence of serious gastrointestinal adverse effects and renal dysfunction associated with traditional NSAIDs, selective COX-2 inhibitors, also named "coxibs", such as rofecoxib and celecoxib, were developed as presented by Langford.[4] The novel COX-2 inhibitors with improved biochemical selectivity recently developed include etoricoxib, valdecoxib, parecoxib (the prodrug of valdecoxib) and lumiracoxib.

Although it is widely accepted that NSAIDs are less potent that opioids for the treatment of pain, several NSAIDs provide a documented 30–50% morphine-sparing effect and improve analgesia when coadministered with patient-controlled analgesia (PCA) morphine. Furthermore, Marret *et al.*[5] in a meta-analysis showed that NSAIDs with morphine PCA decreased postoperative nausea and vomiting by 30%, sedation by 29% but had no significant effect on pruritus, urinary retention and respiratory depression. It was also demonstrated that preemptive NSAIDs were of no analgesic benefit when compared with post-incisional administration of these drugs. Finally, clinical

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studies have confirmed that COX-2 inhibitors can produce analgesia similar to non-selective NSAIDs for moderate to severe acute pain.[4]

There are, however, well-recognized gastrointestinal, cardiac, renal and other adverse effects associated with the use of COX-2 inhibitors. As reported by Langford,[4] large outcome and epidemiological studies and postmarketing surveillance data suggest that, while COX-2 inhibitors do confer improved gastrointestinal safety, they are not devoid of gastrointestinal effects during long-term use. Indeed, major concerns pertaining to their safety profile have recently resulted in considerable debate and subsequent withdrawal of two of these drugs: rofecoxib because of cardiovascular problems and valdecoxib because of serious cutaneous adverse reactions.

In an editorial, Topol[6] reviewed the cardiovascular effects (leading to myocardial infarction and stroke) of COX-2 selective compounds that have emerged as a major concern in recent years. Non-selective NSAIDs can inhibit platelet aggregation because of a reversible inhibition of COX activity. However, this may not be the case with new COX-2 inhibitors. Indeed, COX-2 inhibition with coxibs may increase the risk of vascular thrombus formation by upsetting the balance between pro- and anti-platelet aggregation effects: thromboxane A_2 synthesis is primarily a COX-1-induced effect, and prostaglandin I_2 synthesis is a COX-2 effect. These thrombotic properties have been reported after long-term use of rofecoxib and celecoxib but also by Nussmeier *et al.*[7] with valdecoxib and parecoxib in acute pain management following cardiac revascularization surgery. Bainbridge *et al.*[8] have recently reviewed the use of non-selective NSAIDs for analgesia, and report on pain control and morbidity in cardiothoracic surgery. They found that in patients less than 70 yr of age undergoing cardiothoracic surgery, the adjunctive use of NSAIDs with opioids reduces 24-hr visual analogue scale pain score and opioid requirements.[8]

Skin reaction is the second most common unwanted effect of NSAIDs. Patients could present with a variety of skin conditions from mild rashes, urticaria and photosensitivity to more serious and potentially fatal diseases. In susceptible patients, all types of NSAIDs cause acute renal failure due to the inhibition of the biosynthesis of prostaglandins involved in the maintenance of renal blood flow. As presented by Harris[9] both COX isoforms are expressed in the kidney, therefore, COX-2 inhibitors can cause sodium retention and decrease glomerular filtration rate to a similar extent as non-selective NSAIDs in patients at risk for adverse renal effects. Other concerns about the use of NSAIDs and coxibs are the apparent association with congestive heart failure and a small elevation in systemic blood pressure.

Finally, non-selective NSAIDs may increase bleeding during or after surgery. The use of COX-2 inhibitors may in this context be beneficial. Impairment of bone healing by NSAIDs remains a controversial topic but Reuben *et al.*[10] showed that short-term perioperative administration of celecoxib, rofecoxib, or low-dose ketorolac had no significant deleterious effect on non-union. In contrast, the authors demonstrated that higher doses of ketorolac, history of smoking, and two level vertebral fusions resulted in a significant increase in the incidence of non-union following spinal fusion surgery.[10]

2 Acetaminophen (paracetamol)

Acetaminophen is considered as an effective and well tolerated agent in the management of mild to moderate pain. As acetaminophen has none of the renal or cardiovascular side effects that characterize anti-inflammatory drugs, it can be used in both NSAID- and opioid-sparing roles. Alhashemi *et al.*[11] compared *iv* acetaminophen *vs* oral ibuprofen in combination with morphine patient-controlled *iv* analgesia after Cesarean delivery and showed that *iv* acetaminophen is a reasonable alternative to oral ibuprofen. Unfortunately, acetaminophen is not available in the *iv* form in Canada. Romsing *et al.*[12] in a systematic review examined the effects of rectal and parenteral acetaminophen and acetaminophen in combination with NSAIDs for postoperative analgesia. Evidence was found for a clinically relevant analgesic effect of rectal and parenteral acetaminophen. Furthermore, the concurrent use of acetaminophen and an NSAID was superior to acetaminophen alone although there was no evidence that the combination was better than an NSAID alone.[12] Another review of postoperative pain studies done by Hyllested *et al.*[13] comparing acetaminophen (minimum 1 g) with NSAIDs showed that the analgesic efficacy of acetaminophen was comparable to that of NSAIDs in many of the studies reviewed, but overall, NSAIDs seem to be superior for postoperative pain management. However, the efficacy of acetaminophen and NSAIDs seemed to depend on the type of surgery performed. Finally, Remy *et al.*[14] showed that acetaminophen combined with PCA morphine induced a significant morphine sparing effect but did not change the incidence of morphine-related adverse effects in the postoperative period.

It will be interesting to the reader to note that an *iv* formulation of a prodrug of acetaminophen, propacetamol, has been administered to adults as an alternative

to ketorolac in the perioperative period. Propacetamol reduced PCA morphine consumption by 22%–46% in patients undergoing major orthopedic surgery. A new *iv* formulation of acetaminophen, Perfalgan™, which is equivalent to propacetamol but with better injection site tolerance has been developped recently.[3]

Therefore, the very low apparent risk of acetaminophen therapy suggests a highly favourable risk:benefit ratio, which might justify a role for acetaminophen as a near-routine postoperative background analgesic.

3 Local anesthetics

Continuous nerve blockade is the only available medium-to long-term modality that blocks evoked pain. Decreased nausea and vomiting and increased patient satisfaction are consequences of continuous peripheral nerve blocks, whereas other interesting concepts, such as improved rehabilitation and decreased incidence of postsurgery chronic pain syndromes, are currently receiving attention. The article by Boezaart[15] is worth reading in that context. Furthermore, Ilfeld *et al.*[16] has recently reviewed the use of continuous peripheral nerve blocks at home.

The use of liposomal formulations of local anesthetics prolongs analgesic duration and is an attractive new way of local anesthetic delivery as reported recently by Cereda *et al.*[17] Furthermore, local anesthetics may be combined with other adjuvants such as morphine, clonidine, ketorolac or ketamine. Indeed, intra-articular morphine (0.5–1 mg) with bupivacaine provides long-lasting analgesia after knee arthroscopy[1] and Batra *et al.*[18] showed that a bupivacaine/ketamine combination is superior to intra-articular ketamine analgesia following arthroscopic knee surgery.

Finally, wound infiltration with local anesthetics with or without the use of continuous infusions via *sc* catheters are being reassessed as tested recently by Karamanlioglu *et al.*[19]

4 Anticonvulsants

Results from recent clinical trials reviewed by Gilron[20] demonstrate analgesic efficacy, opioid sparing effect, and possible postoperative functional improvement associated with gabapentin. Mujadi *et al.*[21] have shown that preemptive gabapentin reduces postoperative pain and opioid demand following thyroid surgery, whereas Pandey *et al.*[22] have reported that gabapentin provides effective postoperative analgesia whether administered preemptively or post-incision. Other trials also suggest the potential analgesic efficacy of other anticonvulsant drugs including pregabalin, lamotrigine and possibly oxcarbazepine.[20] This was also confirmed in a recent meta-analysis by Seib and Paul[23] showing that gabapentin given preoperatively decreased pain scores and analgesic consumption in the first 24 hr after surgery. However, the clinical significance of this finding has yet to be determined. Furthermore, a significant reduction in the incidence of side effects could not be demonstrated.[23]

5 Ketamine

There is disagreement on the role of ketamine as an analgesic adjuvant in the postoperative setting. Recently, Lebrun *et al.*[24] reported the lack of a preemptive effect of low-dose ketamine on postoperative pain following oral surgery. Furthermore, McCartney *et al.*[25] in a qualitative systematic study reviewing the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia reported nine positive and seven negative studies about *iv* ketamine administration. Furthemore, Elia and Tramèr[26] in a recent meta-analysis reported that when administered intravenously during anesthesia in adults, ketamine decreased postoperative pain intensity up to 48 hr, decreased cumulative 24 hr morphine consumption, and delayed the time to first request of rescue analgesic. However, when assessing the clinical relevance of these potentially beneficial effects, several issues need to be considered and the authors concluded that despite many published randomized trials, the role of ketamine, as a component of perioperative analgesia, remains unclear.[26]

6 Other drugs

Clonidine,[27] neostigmine[28] and magnesium[29,30] also have potential benefits in reducing postoperative pain. The role of cannabinoids in postoperative pain management has been recently evaluated. The conclusions from only four studies show that cannabinoids are not ideally suited to manage postoperative pain, being either moderately effective, not different from placebo or even antianalgesic at high doses as reported by Beaulieu with nabilone.[31]

7 Conclusions

Although opioid analgesics will continue to play an important role during the immediate perioperative period, the adjunctive use of local anesthetic techniques, acetaminophen, NSAIDs and other adjuvants will probably assume a greater role in the postoperative period.

The new COX-2 inhibitors, despite the sound pharmacological basis for their development and the large publicity made about their use, are not "miracle" drugs. They also seem to be associated with adverse effects and although they may represent a safer

alternative to non-selective NSAIDs, their definitive place in postoperative pain management is not yet settled. However, coxibs remain an appropriate choice for patients with low cardiovascular risk but with increased probability of gastrointestinal complications and bleeding.

Specific objectives of this CME module

- To understand the concept of multimodal analgesia.
- To appreciate the differences between non-selective NSAIDs and specific COX-2 inhibitors (coxibs) when used in the perioperative period.
- To be able to decide if non-selective NSAIDs or COX-2 inhibitors are indicated or not.
- To appreciate the effects of classical NSAIDs and the new COX-2 inhibitors on the gastrointestinal tract, the cardiovascular and renal sys tems.
- To become familiar with the use of acetaminophen in postoperative pain management.
- To understand how to use local anesthetics in the perioperative period.
- To realize that other adjuvant analgesics, such as anticonvulsants and ketamine, can be used in the perioperative period.

References

References preceded by an asterisk (*) are freely available on line and are highly recommended for the completion of the Self-Assessment Program (http://www.cja-jca.org/). The other references provide additional information.

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